PALLIATIVE PEARLS
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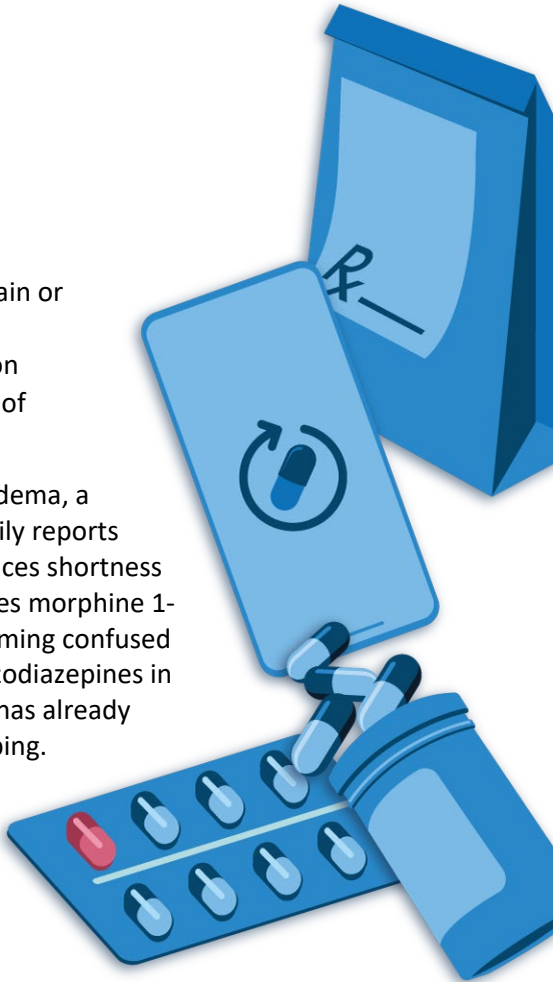
Depression at End of Life Case | March 2021

PATIENT CASE

NW is an 80 year-old female admitted to hospice yesterday with a primary diagnosis of congestive heart failure. Her co-morbidities include hypertension and coronary artery disease. She has allergies to penicillin, which caused a rash, and lorazepam with reported confusion. She was recently started on duloxetine by her family doctor to manage constant worry, irritability and sadness. NW lives with her daughter who also reports that her mother has trouble sleeping due to these recent symptoms.

Current medications:

- Amlodipine (Norvasc®) 5mg; 1 tab po daily for blood pressure
- Carvedilol (Coreg®) 3.125mg; 1 tab po BID for heart failure
- Clopidogrel (Plavix®) 75mg; 1 tab po daily for clot prevention
- Digoxin (Lanoxin®) 0.125mg; 1 tab po daily for heart failure
- Duloxetine (Cymbalta®) 30mg; 1 cap po daily for mood
- Furosemide (Lasix®) 40mg; 1 tab po BID for fluid retention
- Morphine (Roxanol®) 20mg/ml; 0.25ml po/sl every 3 hours PRN pain or shortness of breath
- Spironolactone (Aldactone®) 25mg; 1 tab po daily for fluid retention
- Albuterol (Ventolin®) inhaler; Inhale 2 puffs po q4h PRN shortness of breath



NW's blood pressure is currently controlled and her lower extremity edema, a problem in the past, is being managed well with her diuretics. Her family reports that she gets up to use the bathroom at night frequently. She experiences shortness of breath with activity and uses an albuterol inhaler as needed. She uses morphine 1-2 times per day for pain with good response. She has a history of becoming confused with lorazepam but her family states that she has tolerated other benzodiazepines in the past. The duloxetine, started two weeks ago by her family doctor, has already improved NW's mood, however, she continues to have problems sleeping. Duloxetine is not on the hospice pharmacy's formulary, but the formulary includes several SSRIs.

WHAT ARE SYMPTOMS OF DEPRESSION AT END OF LIFE?

Depression is a medical illness that involves both the mind and body. Hospice patients may face a greater likelihood of developing or worsening a clinical diagnosis of depression due to the awareness of their limited lifespan. Common symptoms include feelings of sadness/unhappiness, irritability, loss of interest/pleasure in normal activities, insomnia or excessive sleeping, changes in appetite or an increased craving for food, and agitation. Other symptoms include slowed thinking or body movements (psychomotor slowing), decreased concentration, fatigue, loss of energy, feelings of worthlessness or guilt, frequent thoughts of death, crying spells and unexplained physical problems. Due to its symptoms, depression has a negative impact on quality of life. Untreated depression leads to significant morbidity and mortality and affects both caregivers and decisions on goals of care. In some people, depression is also associated with an increased desire for hastened death.

WHAT MUST BE ASSESSED BEFORE INITIATING AN ANTIDEPRESSANT?

Before initiating drug therapy, it is important to rule out other factors such as medications or comorbidities that may be causing or worsening depression. Review the medication list and try to relate changes in medication to the onset of the symptoms and rule out other secondary causes:

- Co-morbidities: Anemia, cancer, cardiac disease, endocrine disorders, infections, metabolic disorders, neurological disorders
- Medications: Baclofen, barbiturates, benzodiazepines, beta-blockers, clonidine, corticosteroids, diuretics, opioids
- Other: Alcoholism, psychosocial issues, pain, insomnia

Evaluate patient with DSM-IV criteria or utilize another depression screening assessment tool or simply ask the patient, “Are you depressed?”.[1] Consider the following as a part of a differential diagnosis and recognize that prognosis will affect treatment approaches:[2]

- Major depressive disorder: Treat with drug therapy plus psychotherapy
- Unspecified depressive disorder: Continually assess; may treat with drug therapy plus psychotherapy
- Adjustment disorder with depressed mood: Treat with supportive counseling aimed at coping skills as well as problem solving aimed at resolving or removing stressor
- Grief: Treat with supportive counseling or psychotherapy
- Demoralization: Treat with supportive counseling or psychotherapy

HOW DO I CHOOSE THE RIGHT ANTIDEPRESSANT?[2-4]

Depression may be mediated by the depletion of several neurotransmitters including norepinephrine, serotonin, and dopamine. All antidepressants have similar efficacy, so chose an agent based on patient history and comorbidities, prognosis, side effects and tolerability, potential drug interactions and cost. All agents provide some symptom improvement in the initial weeks of therapy; however, it may take 1-2 months of dose titration and system acclimation for patients to experience the full extent of benefits.

Reserve antidepressants for patients with terminal conditions conducive to longer prognoses. Common undesired effects (or desirable effects in some cases) that may help to distinguish the best agent for your patient include sexual dysfunction, weight gain, sleepiness, energy, anxiety and pain. Note that the monoamine oxidase inhibitor (MAOI) class of antidepressants (phenelzine (Nardil®), tranylcypromine

(Parnate®)) is typically not used as initial therapy in the general population nor initiated in hospice. Please consult your pharmacist for guidance if your patient is taking an MAOI.

Selective Serotonin Reuptake Inhibitors (SSRIs)

- **Agents:** Citalopram (Celexa®), Escitalopram (Lexapro®), Fluoxetine (Prozac®), Fluvoxamine (Luvox®), Paroxetine (Paxil®), Sertraline (Zoloft®)
- **Indicated for:** Prognosis ~ 6 months
- **Consider for:** Concomitant anxiety, psychomotor slowing
- **Avoid/Caution in:** Concomitant agitation, insomnia (particularly fluoxetine), sexual dysfunction concerns
- **Notes:** Citalopram and sertraline have lower potential for drug-drug interactions. Fluoxetine and paroxetine have a higher potential for drug-drug interactions.

Other Agents similar to SSRIs

- **Agent:** Vortioxetine (Trintellix®)
  - **Indicated for:** Prognosis ~ 6 months
  - **Consider for:** Refractory depression, sexual dysfunction concern
  - **Avoid/Caution in:** Nausea concerns
  - **Notes:** Combination serotonin reuptake inhibitor and serotonin receptor antagonist

- **Agent:** Vilazodone (Viibryd®)
  - **Indicated for:** Prognosis ~ 6 months
  - **Consider for:** Refractory depression, sexual dysfunction concerns
  - **Avoid/Caution in:** Nausea concerns
  - **Notes:** Combination serotonin reuptake inhibitor and serotonin receptor partial agonist

Selective Norepinephrine Reuptake Inhibitors (SNRIs)

- **Agents:** Duloxetine (Cymbalta®), Venlafaxine (Effexor®), Desvenlafaxine (Pristiq®), Levomilnacipran (Fetzima®)
- **Indicated for:** Prognosis ~ 6 months
- **Consider for:** Concomitant neuropathic pain, psychomotor slowing, anxiety
- **Avoid/Caution in:** Hypertension, agitation or insomnia, sexual dysfunction concerns

Heterocyclic Antidepressants

- **Agents:** Mirtazapine (Remeron®), Trazodone (Desyrel®)
- **Indicated for:** Prognosis ~ 6 months
- **Consider for:** Concomitant insomnia (mirtazapine, trazodone), appetite loss (mirtazapine), agitation (mirtazapine), sexual dysfunction concerns
- **Avoid/Caution in:** Overweight concerns
- **Notes:** Not considered first-line therapy without concomitant indications for use

Tricyclic Antidepressants (TCAs)

- **Agent:** Amitriptyline (Elavil®), Desipramine (Norpramin®), Doxepin (Sinequan®), Imipramine (Tofranil®), Nortriptyline (Pamelor®)
- **Indicated for:** Prognosis ~ 6 months
- **Consider for:** Concomitant insomnia and/or neuropathic pain
- **Avoid/Caution in:** Structural heart disease, concomitant medications that prolong QT interval
- **Notes:** Not considered first-line therapy; anticholinergic properties may be poorly tolerated by geriatric patients

Aminoketones

- **Agents:** Buproprion (Wellbutrin®, Wellbutrin® SR, Wellbutrin® XL)
- **Indicated for:** Prognosis ~ 6 months
- **Consider for:** Patients with low energy (mild stimulant effects), overweight concerns, sexual dysfunction concerns
- **Avoid/Caution in:** Seizure history (decreases seizure threshold), patients with insomnia
- **Notes:** Adjunct therapy ONLY

Psychostimulants

- **Agent:** Methylphenidate (Ritalin®)
- **Indicated for:** Prognosis ~ 1 month
- **Consider for:** Patients with short prognosis and goals consistent with maintaining alertness and energy level
- **Avoid/Caution in:** Concomitant anxiety, agitation, appetite loss
- **Notes:** Onset within a few days & limited to several-week effectiveness with side effects increasing over time. Most effective for short-term treatment of refractory depression.

Racemic Ketamine S-enantiomer[5,6]

- **Agent:** Esketamine (Spravato®)
- **Indicated for:** Prognosis ~ 1 month
- **Consider for:** Esketamine should only be used for severe treatment-resistant depression in adults after a thorough palliative-case assessment in which other potential diagnoses such as grief or adjustment disorder have been considered
- **Avoid/Caution in:** Hypertension, aneurysm, arteriovenous malformation, intracranial bleeding
- **Notes:** Intranasal formulation; To be taken along with oral antidepressant therapy; Costly

For patients unable to swallow or receiving medications via an enteral tube, consider referring to a recently published PCNOW Fast Facts and Concepts article, titled Non-Oral Pharmacotherapy Options for Depression.[7]

HOW DO I MANAGE SWITCHING FROM ONE ANTIDEPRESSANT TO ANOTHER?

When changing from one antidepressant to another (for example, to a medication included in the hospice formulary), consider the patient's history and prognosis first. If a patient has a history of depression and symptoms have been stabilized on their current medication, it may be more beneficial for the patient to continue that medication, especially if prognosis is days to weeks. If symptoms are new and/or the patient has been on an antidepressant for a short time and prognosis is months, switching agents may be more appropriate. Monitor the patient and adjust the switching strategy for symptoms of withdrawal, side effects, or the return of symptoms of depression.[3,4]

Guide for switching from one agent to another:[3,4,8,9]

1. **Conservative switch or Moderate switch**
    - Gradually decrease and then discontinue the "old" agent followed by a washout period before initiating the "new" agent.
    - Washout periods are drug-specific and should allow time for the discontinued medication to be eliminated from the patient's system. Full elimination is estimated by calculating 5 times the drug's $t_{1/2}$ (elimination half-life, the time it takes for the plasma concentration of the drug in the body to decrease by half), e.g., duloxetine's $t_{1/2}$ averages 12.5 hours so the washout period would be 62.5 hours (approx. 3 days).
    - This approach is not practical or recommended in hospice. Discontinuation of one agent and leaving a gap of time before starting another agent can cause discontinuation syndrome (dizziness, irritability, nausea, fatigue) or symptom recurrence.
    - Discontinuation syndromes are of most concern when switching from a serotonergic agent (e.g., SSRI, SNRI) to a non-serotonergic agent (e.g., heterocyclic, TCA).

2. **Direct or Next Day switch**
    - Appropriate for when the "old" agent and "new" agent are in the same class or similar classes (e.g., SSRIs or SNRIs). Last dose of "old" drug taken one day, and then "new" drug initiated at the same time of day the next consecutive day at a low dose. Gradually increase to effect. Note that Fluoxetine has a long half-life, so wait 4-7 days before starting new agent if fluoxetine is the "old" drug.

3. **Cross-taper switch**
    - Appropriate for when the "old" drug and "new" drug are NOT in the same class and for patients at high risk of symptom/illness relapse. Cross-tapering involves gradually increasing the "new" drug while decreasing the "old" drug so that patient is taking both antidepressants simultaneously.
    - Tapering down "old" agent example: Decrease dose by 25% every week until dose is at a low/initial starting dose (e.g., for "Sertraline 100mg Daily"— Week 1: 75mg/day, Week 2: 50mg/day, Week 3: 25mg/day, Week 4: discontinue)

- Gradually increasing "new" agent example: Increase dose by 25% every week until dose is at therapeutic dose (e.g., for "Mirtazapine"- Week 1: 7.5mg/day, Week 2: 15mg/day, Week 3: 30mg/day, Week 4: Continue 30mg/day if therapeutic or consider increase to 45mg/day)
- Drug-specific notes:
    i. Taper/gradually increase paroxetine over at least 4 weeks
    ii. Taper/gradually increase other SSRIs, venlafaxine, and duloxetine over a total of 1-4 weeks
        - Sertraline or venlafaxine, by 25 to 50 mg/day every 1-2 weeks
        - Paroxetine or citalopram by 5 to 10 mg/day every 1-2 weeks
        - Escitalopram by 5 mg/day every 1-2 weeks
    iii. Literature is lacking for switching to/from vilazodone or vortioxetine to another agent. Consider managing the same as SSRIs due to serotonergic mechanism. Follow manufacturer's recommended titration schedule when starting vilazodone.
    iv. Literature is lacking for switching to/from desvenlafaxine or levomilnacipran to another agent. Consider managing the same as venlafaxine due to similar mechanism of action.

PHARMACIST ASSESSMENT:

NW has cardiac disease in which depression is common. Her medication list contains drugs that may precipitate depression symptoms (carvedilol, furosemide, spironolactone, morphine) however, she has been on these medications for some time now and her depressive symptoms started recently. Her other symptoms, including pain and breathlessness, are generally well controlled. Based on assessment in collaboration with the hospice medical director, it is determined that the patient is experiencing a new onset unspecified depressive disorder. NW has been taking duloxetine for two weeks and her prognosis is estimated to be several months. The hospice wishes to switch to a formulary medication and the family agrees.

RECOMMENDATIONS

1. Assess timing of furosemide dosing to prevent nighttime waking to use bathroom. Consider timing 2nd furosemide dose in the afternoon to minimize nighttime disruption of sleep.
2. NW has had a positive initial response to duloxetine. To minimize discontinuation symptoms, switching to an agent with serotonergic properties will provide a smooth transition.
3. **Direct or Next Day switch:** When patient/family is ready, have NW take the last dose of duloxetine on Day 1. At the same time of day on Day 2, begin citalopram 20mg po daily.

FOR ADDITIONAL INFORMATION ON THIS TOPIC, PLEASE REVIEW THESE REFERENCES:

1. Arnold R. Palliative Care Network of Wisconsin (PCNOW). Fast Facts and Concepts #146: Screening for depression in palliative care. July 2015. Article link
2. Fairman N, Hirst JM, Irwin SA. Clinical manual of palliative care psychiatry. 1st ed. Arlington: American Psychiatric Association; 2016.
3. Clinical Resource, Choosing and Switching Antidepressants. Pharmacist's Letter/Prescriber's Letter. July 2020.
4. Halverson JL. Depression Medication. In: Medscape Drugs & Diseases – Psychiatry. Updated August 6, 2020. Site link
5. Christensen A, Pruskowski J. Palliative Care Network of Wisconsin (PCNOW). Fast Facts and Concepts #384: The Role of Ketamine in Depression. September 2019. Article link
6. Clinical Resource, New Drug: (Spravato) Esketamine. Pharmacist's Letter/Prescriber's Letter. May 2019.
7. Tapper C, Arnold R, Pruskowski J. Palliative Care Network of Wisconsin (PCNOW). Fast Facts and Concepts #372: Non-Oral Pharmacotherapy Options for Depression. January 2019. Article link
8. Keks N, Hope J, Keogh S. Switching and stopping antidepressants. Aust Prescr 2016;39:76–83. PDF link
9. Adetokunboh-Ajala M. MIMs guidance on switching and withdrawing antidepressants updated. MIMs. February 8, 2016. Site link
10. Clinical Pharmacology [database online]. Tampa, FL: Elsevier/Gold Standard, Inc.; 2021.